REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.111, are respectfully requested.

By the foregoing amendment, the specification has been amended to include reference to prior applications to which benefit of priority has been claimed. The specification has been further amended to insert appropriate notations with respect to trademarks used in the specification and to correct several minor clerical type errors. Additionally, claims 1-18 have been canceled, without prejudice or disclaimer to the subject matter recited therein, and new claims 19-38 have been added. Support for new claim 19 can be found throughout the application including at least in previous claims 1 and 7, on page 9, lines 9-13, and on page 27, lines 5-7. Support for new claim 20 can be found at least on page 9, lines 14-15. Support for new claim 21 can be found at least on page 9, line 16. Support for new claim 22 can be found at least on page 12, lines 15-17. Support for new claim 23 can be found at least in previous claims 12 and 14. Support for new claim 24 can be found at least from page 9, line 35 to page 10, line 3. Support for new claim 25 can be found at least on page 10, line 4. Support for new claim 26 can be found at least on page 10, lines 26-28. Support for new claim 27 can be found at least in previous claim 8. Support for new claim 28 can be found at least in previous claim 15. Support for new claim 29 can be found at least in previous claim 16. Support for new claim 30 can be found at least on page 10, lines 30-33, and on page 14, lines 8-9. Support

for new claim 31 can be found at least on page 10, lines 34-35. Support for new claim 32 can be found at least in previous claims 9 and 18. Support for new claim 33 can be found at least in previous claim 10, and page 14, lines 30-34. Support for new claim 34 can be found at least on page 15, lines 1-5. Support for new claim 35 can be found at least on page 16, lines 4-6. Support for new claim 36 can be found at least in previous claims 17 and 18. Support for new claim 37 can be found at least on page 20, lines 10-11. Support for new claim 38 can be found at least in Example 4. Thus, no new matter has been added.

Turning now to the Official Action, the Examiner has indicated that the previous restriction requirement was been withdrawn and claims 1-18 were examined together. As noted above, claims 1-18 have been canceled, without prejudice or disclaimer to the subject matter recited therein, and new claims 19-38 have been added.

Next, the Examiner noted that (i) the first line of the specification should: include specific reference to earlier applications to which benefit of priority is being claimed; and (2) use of trademarks in the specification should be capitalized or properly notated wherever they appear. As discussed above, the specification has been amended to satisfy both of these requirements. It is noted with regard to the priority claim that an application data sheet is not believed to be necessary since such information is included in the Combined Declaration and Power of Attorney.

Claims 1-8 and 11-16 have been rejected under 35 U.S.C. § 112, second paragraph as being incomplete for allegedly omitting essential steps. This rejection is respectfully

traversed. However, to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, claims 1-18 have been canceled. Thus, the Examiner's rejection has been mooted. New claims 19-38 are believed to satisfy the requirements of, *inter alia*, 35 U.S.C. § 112, second paragraph.

Claims 1, 9-11 and 17-18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Shabram (WO 96/27677). This rejection is respectfully traversed.

Since claims 1-18 have been canceled, this rejection is rendered moot. Further, the Shabram PCT publication ("the Shabram PCT") fails to anticipate the presently claimed invention. The Federal Circuit has held that for prior art to be anticipatory, every element of the claimed invention must be disclosed in a single item of prior art in the form literally defined in the claim. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 213 U.S.P.Q. 81, 90 (Fed. Cir. 1986). This requirement for anticipation has clearly not been met with respect to the currently pending claims.

The presently claimed invention is directed to a method of purifying recombinant adenoviruses from a crude viral preparation (e.g., a cell lysate) comprising at least one chromatographic step performed under fluidized bed conditions using particles of adsorbent that comprise an agarose matrix, a central quartz core and dextran chains covalently coupled to said agarose matrix, on which are attached positively charged groups, wherein the yield of adenoviral particles eluted after the fluidized bed chromatography is at least 80%. The specification and the working Examples illustrate a fluidized-bed anion exchange chromatographic process performed on a Streamline® resin which is an

agarose/quartz base matrix to which are attached dextran chains covalently coupled to positively charged ligands (e.g., the quaterny amino Q groups). The overall yield of adenoviral particles reaches approximately 80% or more after the fluidized bed chromatography step (see Table on the bottom of page 26, page 27, lines 5-7 and Table on page 30). The high virus yield provided by the process of the present invention makes it compatible with industrial production.

The Shabram PCT, on the other hand, discloses a method of purifying recombinant adenoviruses from a cell lysate comprising two chromatography steps, one being an anion exchange chromatography and the second one being either an immobilized metal ion affinity (claim 1) or a hydrophobia interaction (claim 20) chromatography. The Shabram PCT mentions, on page 9, line 15, the possibility of performing the chromatographic step(s) in fluidized bed columns, while only illustrating conventional packed bed (i.e., gravity) columns. The working Examples of the Shabram PCT describe a two step protocol consisting of submitting a clarified cell lysate obtained from adenovirus infected cells to a DEAE anion exchange chromatography (gravity column), and the resulting DEAE eluate to an immobilized zinc affinity chromatography (IZAC). As evidenced in Table 1, the yield of total particles recovered after conventional DEAE chromatography is 67% ($3x10^{12}$ particles loaded to DEAE column and $2x10^{12}$ particles recovered into the DEAE eluate) and the yield of total particles recovered after IZAC chromatography is 47% ($1.52x10^{12}$ particles loaded to IZAC column and $0.714x10^{12}$ particles recovered into the IZAC eluate).

Therefore, the process of the presently claimed invention is patentably distinguishable from the Shabram PCT by at least the type of adsorbent particles used and the better overall viral yield recovered. Since each and every element of the presently claimed invention is not taught by the Shabram PCT, the Shabram PCT fails to anticipate the claimed invention. Accordingly, withdrawal of this rejection is respectfully requested.

Finally, claims 2-8 and 12-16 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Shabram PCT as applied above, and further in view of Hjorth (*Trends in Biotech.*, 1997, 15:230-5) and Shabram et al. (U.S. Patent No. 5,837,520) (hereinafter "the Shabram U.S. Patent").

Claims 1-18 have been canceled thus rendering this rejection moot. Furthermore, this rejection fails to establish a proper *prima facie* case of obviousness against the currently pending claims. In particular, the combination of references as cited by the Examiner fail to teach or suggest the presently claimed invention.

It is noted that the Shabram PCT and the Shabram U.S. Patent both have the same specification, despite the Examiner's comments in the Official Action. Thus, as discussed above, both Shabram documents fail to teach at least the type of adsorbent particles used in the presently claimed invention and the better overall viral yield recovered with regard to the presently claimed invention.

The Hjorth reference fails to remedy the serious deficiencies of the Shabram documents. Hjorth relates to the purification of recombinant proteins from cell culture and homogenates using fluidized bed chromatography. In this regard, Hjorth discloses a series

of resins that can be used to recover proteins in fluidized-bed processes, including agarose/quartz based matrix to which is attached the positively charged ligand (e.g., DEAE). However, Hjorth fails to disclose that fluidized bed chromatography can be used for purifying viral particles, and especially adenoviral particles, resulting in a yield of infectious particles reaching at least 80%. Furthermore, Hjorth fails to disclose the use of agarose/quartz base matrix having dextran chains covalently coupled to the agarose matrix, on which are attached positively charged group (e.g., Streamline® resin).

Since the combination of references fails to teach or suggest the presently claimed invention, withdrawal of this rejection is respectfully traversed.

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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